RHEUMATOLOGY

Rheumatology 2015;54:1420–1428
doi:10.1093/rheumatology/kev004
Advance Access publication 3 March 2015

Original article

Long-term experience with rituximab in anti-synthetase syndrome-related interstitial lung disease

Helena Andersson[1,2], Marthe Sem[2], May Brit Lund[3], Trond Mogens Aaløkken[4], Anne Günther[4], Ragnhild Walle-Hansen[5], Torhild Garen[2] and Øyvind Molberg[1,2]

Abstract

Objective. To retrospectively evaluate the efficacy and safety of rituximab (Rtx) treatment in patients with anti-synthetase syndrome (ASS) and severe interstitial lung disease (ILD).

Methods. Patients with severe ILD and >12 months follow-up post-Rtx were identified from the Oslo University Hospital ASS cohort ($n = 112$). Clinical data, including pulmonary function tests (PFTs), were retrospectively collected from medical reports. Extent of ILD pre-, and post-Rtx was scored on thin-section high-resolution CT (HRCT) images and expressed as a percentage of total lung volume. Muscle strength was evaluated by manual muscle testing of eight muscle groups (MMT8).

Results. Altogether, 34/112 ASS patients had received Rtx; 24/34 had severe ILD and >12 months follow-up post-Rtx (median 52 months). In these 24 patients, the median percentage of predicted forced vital capacity, forced expiratory volume in 1 s (FEV1) and diffusing capacity of the lungs for carbon monoxide (DLCO) increased by 24%, 22% and 17%, respectively, post-Rtx. Seven patients (all with disease duration <12 months and/or acute onset/exacerbation of ILD) had >30% improvement in all three PFTs. HRCT analysis showed a median 34% reduction in ILD extent post-Rtx. MMT8 score increased post-Rtx. During follow-up, 7/34 (21%) Rtx-treated ASS patients died; 6/7 deaths were related to infections. The mortality rate in the Rtx-treated group was comparable to that of the remaining ASS cohort (25/78 deceased; 32%).

Conclusion. This study, which included 24 Rtx-treated ASS patients with severe ILD, reports improved PFTs after a median 52 months follow-up post-Rtx. The best outcome was observed in patients with a disease duration <12 months and/or acute onset/exacerbation of ILD. The study indicates that Rtx could be a treatment option for selected ASS patients, but infections should be given attention.

Key words: rituximab, anti-synthetase syndrome, myositis, anti-aminoacyl tRNA synthetase, anti-Jo1, interstitial lung disease.

CLINICAL SCIENCE

Rheumatology key messages

- Rituximab is a treatment option in anti-synthetase syndrome-related interstital lung disease.
- Rituximab was most effective in recent onset anti-synthetase syndrome with acute-onset interstitial lung disease.

Introduction

The anti-synthetase syndrome (ASS), first described by Marguerie and coworkers in 1990 [1], is characterized by the presence of anti-aminoacyl tRNA synthetase (aaRS) autoantibodies, PM/DM, interstitial lung disease (ILD), RP, arthritis, and mechanic's hands. At present eight different anti-aaRS antibodies have been identified, the most common being anti-Jo1, directed against histidyl-tRNA synthetase and found in ~20–30% of all myositis patients [2]. The clinical phenotype of the syndrome seems to depend on which one of the anti-aaRSs is present; the frequency of myositis varies somewhat between the different anti-aaRSs, whereas ILD appears to be present in the vast majority of patients with ASS, the highest proportion being seen in patients with non-anti-Jo1 aaRS antibodies [3–5]. Importantly, ILD in ASS is associated with

[1]Institute of Clinical Medicine, [2]Department of Rheumatology, [3]Department of Respiratory Medicine, [4]Department of Radiology and [5]Department of Orthopaedic Surgery, Oslo University Hospital, Oslo, Norway

Submitted 7 April 2014; revised version accepted 13 January 2015

Correspondence to: Helena Andersson, Institute of Clinical Medicine, Department of Rheumatology, Oslo University Hospital, PO Box 4950 Nydalen, Oslo 0424, Norway.
E-mail: helena.andersson@medisin.uio.no

morbidity and mortality [6, 7]. Hence, effective treatment for ILD is one of the major clinical challenges in ASS.

In case reports, many different immunomodulatory drugs, including AZA, CYC, cyclosporin, MMF and tacrolimus, have been evaluated in ASS patients, all with observed effects on the ILD component [8–12].

During the last decade, rituximab (Rtx), an anti-CD 20^+ mAb, has been used in the treatment of a variety of rheumatic inflammatory conditions. Several small retrospective studies have shown at least partial benefit of Rtx in refractory PM/DM, ASS included [13–15]. However, the controlled randomized study of 195 Rtx-treated patients with refractory myositis did not show any statistical difference between the two treatment arms for primary and secondary endpoints [16]. But, interestingly, when further analysing data from this study, the authors found that patients with anti-aaRS antibody had predictably shorter time to improvement compared with patients without myositis-specific antibodies. In the same study, there was also a trend towards an association of improvement in patients with reduced lung function [17].

So far there have been few reports published on ASS-associated ILD treated with Rtx. Marie *et al*. [18] showed an increase in forced vital capacity (FVC)/diffusing capacity of the lungs for carbon monoxide (DLCO) and a decrease/stabilization in the extent of ILD for seven Rtx-treated ASS patients with refractory ILD, with a follow-up of at least 12 months. A significant increase in FVC at 12 weeks post-Rtx for two anti-Jo1-positive patients with DM was seen in the pilot study of Levine [19]. Nalotto *et al*. [20] described a significant increase in DLCO 6 months post Rtx in a patient with ASS and progressive ILD.

In a recent consensus report on outcome measures in CTD-associated ILD, FVC and the total extent of ILD on HRCT were defined as appropriate core domains for clinical trials [21]. Data on ILD extent in ASS are limited, but there are a number of case reports using other CT evaluation methods [22].

From our tertiary referral hospital, we reported a short-term beneficial effect of Rtx in 11 patients with ASS-associated ILD [23]. In the current study, we present long-term follow-up data on pulmonary function tests (PFTs) and the extent of ILD (as indicated by HRCT) in those patients, and in an additional 19 patients with ASS-associated ILD. In all these patients, the main indication for Rtx treatment was severe ILD, but two-thirds of the patients also had signs of myositis. Hence, data on muscle function pre- and post-Rtx treatment will also be presented.

Patients and methods

Study population

Patients from Oslo University Hospital (OUH) diagnosed between 1994 and 2013 with a positive serological test to aaRS antibodies, the presence of ILD defined by the American Thoracic Society (ATS) criteria [24], and/or probable or definite myositis according to Bohan and Peter criteria [25] were defined as ASS ($n = 112$). Of these patients, 34 were treated with Rtx, 30/34 with severe ILD as the treatment indication and 24/30 with a follow-up of >12 months. Severe ILD was defined by FVC $<70\%$ of predicted, and/or DLCO $<60\%$ of predicted, and/or patients who needed mechanical respiratory support. The patients were classified with acute or gradual onset of ILD, according to the definition by Tillie-Leblond *et al*. [26]. The study was approved by the regional committee of health and medical research ethics in South-East Norway.

Serum antibody assays

Serum anti-Jo-1 and anti-SSA were detected by automated ELISA (EliA, Phadia; Freiburg, Germany). Anti-Jo-1, anti-threonyl-(PL-7), anti-alanyl-(PL-12), anti-glycyl-(EJ) and anti-isoleucyl-(OJ) tRNA synthetase antibodies were detected by a commercial immunoblot assay (Euroline Myositis kit, Euroimmune Laboratory, Luebeck, Germany).

PFTs

PFT analyses included FVC, FEV1 and DLCO (uncorrected for alveolar volume), all three being expressed as a percentage of expected reference values [27]. According to an international consensus statement of the ATS on idiopathic pulmonary fibrosis, improvement in FVC of $\geqslant 10\%$ and/or DLCO of $\geqslant 15\%$ was defined as clinically significant [24].

HRCT images

Low-dose thin-section CT images were obtained in the supine position during breath-holding and deep inspiration taken a median 0 months (range 0–3) before Rtx and a median 5 months (range 3–12) after Rtx treatment. The images were reconstructed both from 1 to 1.25-mm thick sections at 10-mm intervals and from 2.5-mm contiguous images, then reviewed in random order by two chest radiologists (A.G. and T.M.A.). The observers, blinded to the patient's clinical condition, evaluated the presence/extent of ILD. These findings included ground-glass opacity, interlobular septal thickening, airspace consolidation, and reticular pattern [28].

The percentage of lung parenchyma with an ILD component was evaluated independently for each thin-section image. Volumes were precisely measured by drawing freehand regions of interest on the screen [29]. Thus, observers were able to score the overall extent of ILD, and relate this to the total volume of lung parenchyma.

Myositis evaluation

Myositis parameters included plasma creatinine kinase (CK) values and the manual muscle test for eight muscles (MMT8) [30]. CK values were recorded 0–2 months pre-Rtx and 3–6 months post-Rtx. CK above the upper reference value of the OUH laboratory (>150 U/l) was defined as abnormal. MMT8 measurements were performed by a physiotherapist. Since three patients (#1, #21 and #28) were not able to perform MMT8 adequately, the test was measured as a percentage of the

total possible score. In all but two patients (#4, #10), the test was performed 0–2 months pre-RTX and 3–7 months post-Rtx.

Serious adverse events and mortality

Deaths were registered throughout the observation period and not only in connection with the Rtx infusions. Serious adverse events (SAEs) were defined as events requiring hospitalization, registered 0–20 weeks after being given the Rtx infusion.

Statistical analysis

PFT, affected lung parenchyma in HRCT images, CK and MMT8 values pre- and post-Rtx treatment were compared using the Wilcoxon signed-rank test, with the significance level set at $P < 0.05$.

Results

Treatment indications and clinical characteristics

From 2006 to 2013, 34 of the 112 ASS patients followed at OUH received at least one infusion of Rtx. The treatment indications for Rtx were severe, progressive and/or therapy-resistant lung disease (30 cases), severe arthritis (2 cases), myositis (1 case) and lymphoma (1 case). In the 33 cases with ASS-related indications, plenary discussions at the Department of Rheumatology were undertaken before Rtx was initiated.

Of the 30 patients who received Rtx due to ILD, 6 had <12 months follow-up; leaving 24 patients (7 males, 17 females) eligible for the long-term follow-up analyses (Table 1). Short-term follow-up data for 9 of the 24 patients were published in 2009 [23]. The 24 patients with >12 months follow-up had median disease duration of 84 months (23–440), 19 were anti-Jo-1-positive, three anti-PL-7 and two anti-PL-12-positive (Table 1). Anti-SSA was present in 18/24 patients (75%). Acute onset/exacerbation of ILD was evident in 50% of the patients, and two patients were diagnosed with pulmonary hypertension (#11, #13). One of these patients (#13) later received a bilateral lung transplant. Myositis and arthritis were diagnosed in 79% and 13% of the patients, respectively. One patient presented with necrotizing digital ulcers (#20).

Rtx treatment

Time from disease onset to first Rtx infusion varied between 1 and 330 months (median 15 months). Median follow-up from the first Rtx infusion was 52 months (range 12–118) (Table 1). The first cycle of Rtx treatment was given as one infusion of 1000 mg on each of days 0 and 14, except for three patients (#1, #7 and #11). Patients #7 and #11 were treated according to standard lymphoma protocol ($4 \times 375\,mg/m^2$), while patient #1 was treated with a reduced dose because of perceived infection risk. The mean number of Rtx cycles was 2.7 (range 1–11), but 8/24 patients were treated with only one cycle during the observation period (Table 1). Four patients (#15, #17, #23 and #31) were only treated with one infusion of 1000 mg of Rtx on the last cycle. None of the patients were treated with Rtx as monotherapy, but 6/24 patients did not receive any other immunosuppressive therapy prior to Rtx (Table 1).

PFTs

PFTs obtained prior to the first infusion of Rtx were available in 21/24 patients (Fig. 1). The median percentage of predicted FVC increased from 58% (range 15–60) at the first Rtx treatment to 72% (range 38–105) at the last follow-up visit—an increase of 24% ($P < 0.018$). The median percentage of predicted FEV1 increased by 22%, from 58% (range 35–107) to 71% (range 31–115) at follow-up ($P < 0.037$). The increase in the median percentage of predicted DLCO was 17%, from 41% (range 15–60) to 48% (range 15–84) at follow-up ($P < 0.025$) (Fig. 2). Hence, improvements in both FVC and DLCO achieved clinical significance as defined by the ATS. Seven of the 24 patients (#2, #4, #8, #12, #18, #20 and #28) responded with >30% increase in all three parameters (patients marked by superscript 'a' in Table 1). In this group, all but one patient were treated with Rtx within a year after the onset of symptoms, and 4 of 6 were naive to immune-modulating therapies prior to the first Rtx cycle (Table 1).

HRCT images

HRCT images taken pre- and post-Rtx treatment were available for 23/24 patients (except for #33). The median volume of total lung parenchyma with ILD changes was 50% (range 25–100) pre-Rtx. After Rtx treatment, the extent of ILD was decreased to a median 33% (0–93), ($P < 0.001$) (Fig. 3). In five patients, the ILD-component decreased >60% (#5, #12, #18, #20, #28: patients marked by a superscript 'b' in Table 1). One patient (#13) had an increase in the extent of ILD, from 55% pre-Rtx to 88% post-Rtx (Fig. 3). This patient later received a lung transplant.

Myositis evaluation

CK values above the upper reference level (150 U/ml) were noted in 16/24 patients 0–2 months prior to the first Rtx infusion, and 4/24 patients 3–6 months post-Rtx (Fig. 4). The median CK value pre-Rtx was 990 U/l (range 157–7140) and the corresponding post-Rtx value was 88 U/l (range 31–1956), ($P < 0.002$). MMT8 data were retrievable for 15/24 patients. MMT8 increased from a median 93% of the maximum score pre-Rtx to a median 98% post-Rtx ($P < 0.05$) (Fig. 4). Further analyses showed that 4of 15 patients with available MMT8 data had normal CK levels pre-Rtx but reduced muscle strength (#10, #15, #19 and #20). Conversely, there were also four patients who had CK >150 U/ml, but scored maximum on MMT8 (#4, #5, #8 and #18) (Fig. 4).

Anti-Jo-1 levels

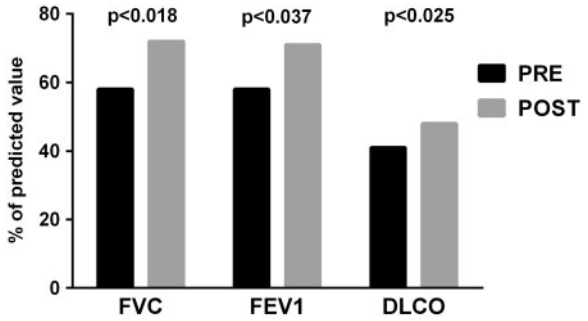
Of the 19 patients, 17 had serum anti-Jo-1 detected by ELISA, and 2 patients had anti-Jo-1 detected by immunoblot assay (#21, #33). In 9 of 17 patients, titres of anti-Jo-1

Table 1 Patient characteristics and treatments

ID/age/sex	Anti-aaRS	Acute onset/exacerb. of ILD	Total disease duration, months	Time from first Rtx, months	Rtx Cycles, *n*	Medication before first Rtx	Medication after first Rtx	Other clinical symptoms	SAE	Vital status	Cause of death
1/60/M	Jo-1	Yes	23	22	2	None	CYC, GC > 10 mg	Myositis	Sepsis	D	Endocarditis
2/47/F[a]	Jo-1	Yes	440	80	4	AZA, CSA, CYC	AZA	Myositis	Purpura	A	
4/69/M[a]	Jo-1	Yes	104	92	1	CYC, AZA, GC > 10 mg	AZA, GC < 10 mg	Myositis		A	
5/44/K[b]	Jo-1	Yes	75	73	2	None	CYC, HQC, MMF, GC	Myositis		A	
6/28/K	PL-12	No	197	118	4	GC > 10 mg, CSA, HCQ, AZA	GC < 10 mg			A	
7/37/M	Jo-1	No	120	74	1	CYC, CSA, TAC, INF, IVIG, GC > 10 mg	AZA, MMF, GC > 10 mg, IVIG	Myositis	Abscess	D	*Pneumocystis*/ psychiatric condition
8/66/K	Jo-1	No	101	82	1	CYC, GC > 10 mg	AZA MMF, GC < 10 mg	Myositis		A	
10/69/K	Jo-1	No	98	80	1	CYC, CSA, GC > 10 mg	AZA, MMF, GC < 10 mg	Myositis		A	
11/58/K	Jo-1	No	44	12	1	CYC, CSA, TAC, AZA, GC > 10 mg	AZA, MMF, GC > 10 mg	Myositis, PH		D	Heart-failure
12/56/K[a,b]	Jo-1	Yes	36	32	1	None	CYC, AZA, GC > 10 mg	Myositis		A	
13/57/M	Jo-1	No	105	61	2	CYC, AZA, GC > 10 mg	CYC, AZA, MMF, CSA, GC < 10 mg,	Myositis, PH, Tx		D	Infection/rejection
15/41/K	PL-12	No	108	34	4	MTX, AZA, SSZ, GC > 10 mg	MMF, CYC, GC 10 mg	Arthritis		A	
16/46/M[a]	PL-7	Yes	65	57	2	CYC, GC > 10 mg	CYC, MMF, GC < 10 mg, IVIG	Myositis		A	
17/46/K	Jo-1	No	96	56	6	AZA, GC > 10 mg	CYC, CSA, MMF, GC < 10 mg	Myositis, Arthritis	Neutropenia, Sepsis	A	
18/34/M[a,b]	Jo-1	Yes	51	46	2	None	CYC, AZA, MMF, GC > 10 mg	Myositis		A	
19/56/K	Jo-1	No	44	35	6	CYC, HCQ, GC > 10 mg	AZA, GC < 10 mg	Myositis		A	
20/69/K[a,b]	PL-7	Yes	48	46	1	None	CYC, AZA, GC	Vascular ulcers		A	
21/71/K	Jo-1	No	102	57	3	AZA, GC > 10 mg	CYC, MMF, GC	Arthritis		A	
23/55/M	PL-7	No	93	24	3	GC > 10 mg, AZA, CYC, MMF	GC 10 mg			A	
24/61/K	Jo-1	Yes	26	23	2	GC > 10 mg	CYC, AZA, GC > 10 mg	Myositis		A	
28/78/K[a,b]	Jo-1	Yes	49	47	1	None	CYC, GC > 10 mg, AZA	Myositis			
31/55/K	Jo-1	No	101	75	11	AZA, CYC, GC > 10 mg, MMF	AZA, MMF, GC > 10 mg	Myositis	*Pneumocystis*	A	
32/60/K	Jo-1	Yes	41	37	3	None	CYC, AZA, MMF, IVIG, GC < 10 mg, TAC,	Myositis		A	
33/57/K	Jo-1	Yes	38	30	2	None	CYC, GC > 10 mg, AZA MMF, IVIG, PP	Myositis	*Pneumocystis* Sepsis	A	
Disease duration <12 months											
3/66/M	Jo-1	No	52	8	1	GC > 10 mg	GC < 10 mg	PH		D	Infection/ heart-failure
9/60/K	Jo-1	Yes	27	3	1	GC > 10 mg	CYC, GC > 10 mg	Myositis	*Pneumocystis*	D	Infection
25/41/K	Jo-1	No	102	6	1	GC > 10 mg	HCQ			A	
26/39/K[a]	Jo-1	Yes	11	7	1	None	CYC, GC > 10 mg, AZA, MMF	Myositis		A	
30/44/M[a]	Jo-1	Yes	18	11	1	CYC, GC > 10 mg	TAC, GC			A	
34/72/M	Jo-1	No	69	11	2	GC > 10 mg, AZA, MMF	GCC > 110 mg	Myositis		D	Infection/ pulmonary cancer

[a]Patients with >30% increase in FVC, FEV1 and DLCO post-Rtx. [b]Patients with >60% decrease in extent of ILD in HRCT images post-Rtx. GC: glucocorticoids; INF: infliximab; PH: pulmonary hypertension; PP: plasmapheresis; TAC: tacrolimus; Tx: transplantation; A: alive; D: dead.

Fig. 1 Pulmonary function tests



Median changes in pulmonary function measured as forced vital capacity (FVC), forced expiratory volume in 1 s (FEV1) and unadjusted diffusing capacity of the lungs for carbon monoxide (DLCO), pre- and post-Rtx treatment for 24 ASS patients with a median follow-up time of 52 months. Details of pulmonary function tests on individual patients are available in Fig. 2.

taken 0–3 months prior to Rtx and 2–6 months after treatment were available. In all these nine patients, anti-Jo-1 levels decreased following treatment, with a median decrease for the whole group of 33% ($P < 0.008$) (Fig. 5).

Immunomodulatory therapies

In total, 18 of 24 patients had failed other immunosuppressive treatment prior to the first Rtx infusion (Table 1). In 7 of 24 patients, Prednisolone was tapered from >10 mg daily to <10 mg daily following Rtx (Table 1). All but two patients (#6 and #23) either continued or started immunomodulatory therapy after the first Rtx cycle. In patients starting new immunomodulatory drugs, treatment was initiated 0–3 months post-Rtx treatment. Of the 12 patients receiving Rtx due to acute onset/exacerbation of ILD, 10 received combined induction therapy with Rtx and i.v. CYC.

Mortality and SAEs

Altogether, there were 7 deaths among the 34 Rtx-treated ASS patients, six 6 of which were probably caused by infection, all but one occurring >6 months after the last Rtx infusion (#9; *Pneumocystis jirovecii* pneumonia, registered 2 months post-Rtx). All deaths and SAEs were noted in the 30 patients with severe lung disease. During the observation period, seven non-fatal SAEs were identified, six of them infections. The non-infectious SAE was a purpural rash developing in direct connection with the Rtx infusion. Three of the six infectous SAEs were caused by *P. jirovecii* (Table 1). All of the six infection-related SAEs occurred 1–20 weeks after the last infusion of Rtx.

Discussion

Severe lung disease is a major determinant of morbidity and mortality in ASS. Here, we performed retrospective analyses of 24 Rtx-treated ASS patients with ILD and a median follow-up time of 52 months. Significant improvements, both in PFT and ILD extent in HRCT images were noted, indicating that Rtx could have effects on the ILD component in this patient group.

Interestingly, the most pronounced effects on lung function were noted in patients with disease duration <12 months at the first Rtx cycle and/or acute onset/exacerbation of ILD. In this group, seven patients increased >30% in FVC, FEV1 and DLCO during the observation period. One additional patient (#5) also had a >30% increase in FVC and FEV1 post-Rtx, but corresponding DLCO data were not retrievable. Furthermore, among the six patients with follow-up of <12 months (Table 1, lower panel), two patients (#26 and #30) with <1 year disease duration increased >30% in FVC, FEV1 and DLCO following Rtx (data not shown). Taken together, these results suggest that Rtx treatment may be most beneficial in ASS patients with disease duration <12 months and/or acute onset/exacerbation of ILD.

The HRCT analyses showed that the extent of ILD decreased post-Rtx in the majority of the ASS patients. This is consistent with other earlier case series/reports [18, 23, 31, 32]. In the current study, the total extent of ILD was scored without pattern differentiation. Hence, no suggestion of specfic ILD patterns in ASS was made.

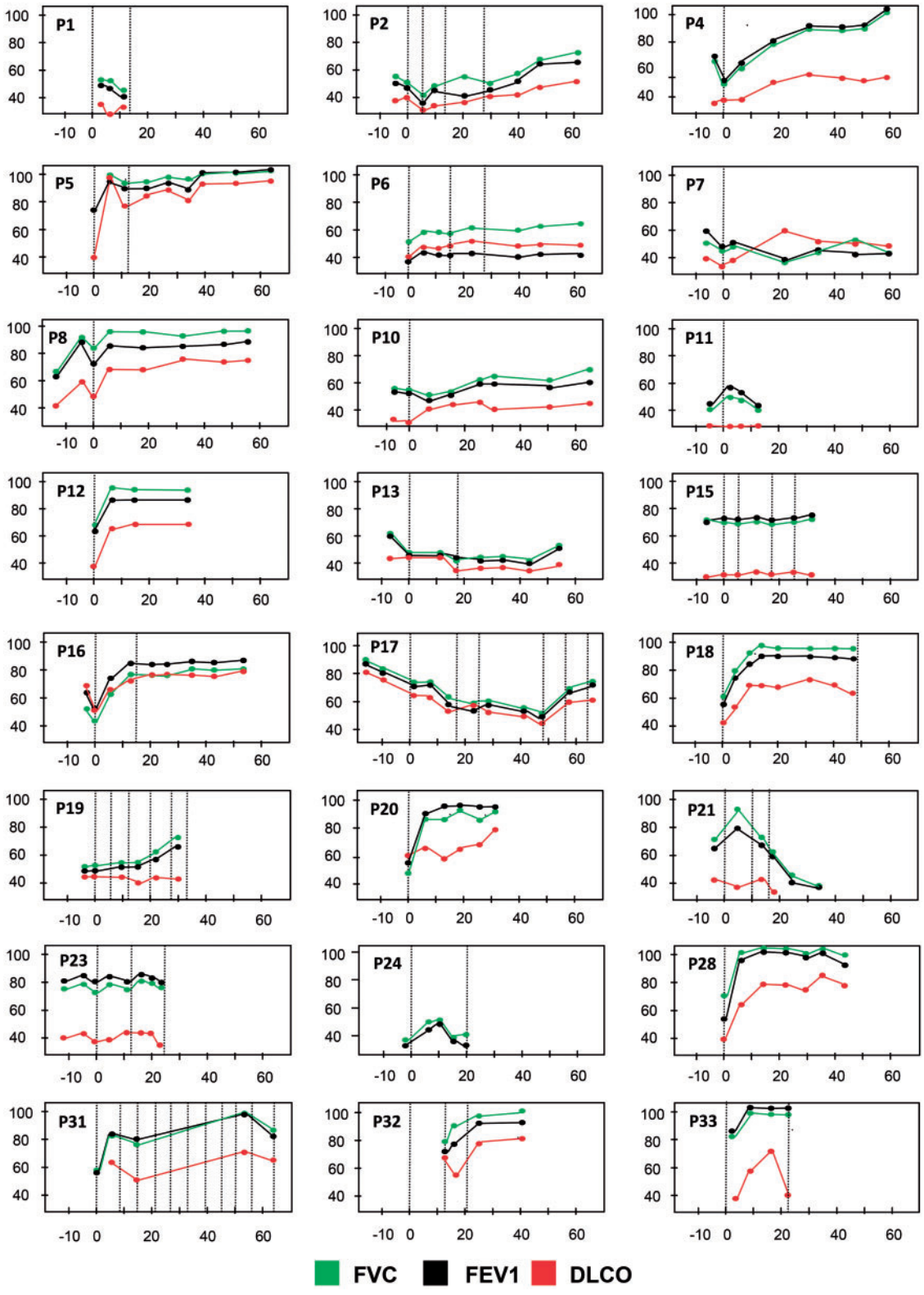
The primary indication for Rtx treatment in the 24 patients reported was severe ILD, but two-thirds of the patients also had signs of myositis, with elevated CK levels and/or reduced MMT8 scores. Although our muscle evaluation data have limitations (e.g. large variation in CK level, different interpreters of the MMT8 test) and there was only a moderate increase in MMT8 post-Rtx, the results support previous notions of Rtx effects on the muscle component of ASS [14, 16].

Since Rtx treatment is associated with infections, and ILD in itself carries increased infection risk, it was not surprising that most SAEs were related to infections. Notably, Rtx was probably not the only factor contributing to the increased risk of infections; as many as 75% of the patients were on other immunomodulatory drugs prior to the first Rtx cycle, and all but two patients received other maintenance therapy after the Rtx treatment. All six patients with infection-related SAEs were treated with i.v. CYC either prior to or directly after the first Rtx cycle. Thus, infection prevention with antibiotic therapy for ASS-associated ILD patients treated with Rtx and/or CYC can be considered.

In total, 21% (7/34) of the patients died during the observation period, most of the deaths being related to infections. In comparison, the mortality rate for the total OUH ASS cohort with a median disease duration of 98 months (range 2–378) was 32% (25 of 78). Hence, the mortality rate did not appear to be higher in the Rtx-treated group than in non-Rtx-treated ASS patients from the same geographical area. Taken together, our data seem to be consistent with other studies reporting increased overall mortality for ASS, with ILD as the major determinant of mortality [33, 34].

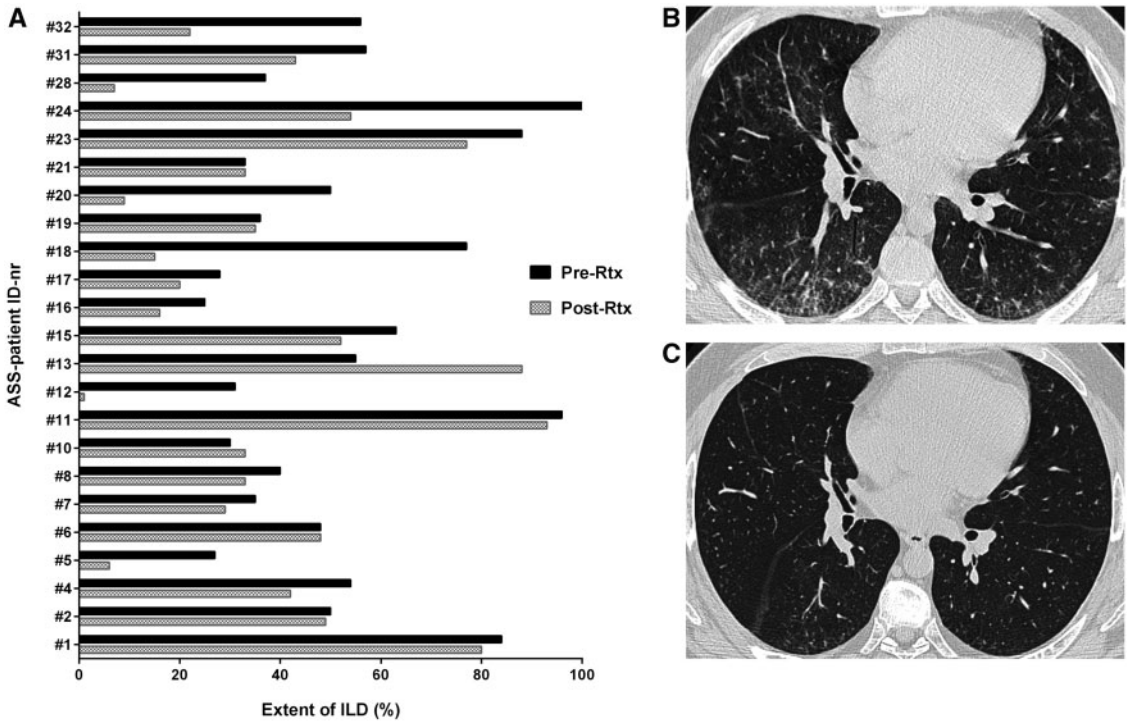
All patients with available anti-Jo-1 titres ($n = 9$) before and after treatment displayed significant titre reductions

FIG. 2 Longitudinal changes in pulmonary function and diffusion capacity in 24 anti-synthetase syndrome patients treated with rituximab



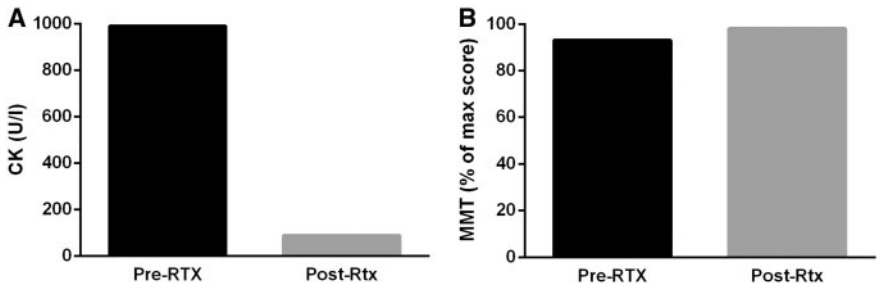
The panels show the development of forced vital capacity (FVC), forced expiratory volume in 1 s (FEV1) and unadjusted diffusing capacity of the lungs for carbon monoxide (DLCO) in a period ranging from 10 months prior to the first rituximab infusion to 60 months after this infusion. The stapled vertical lines indicate the timing of repeated rituximab treatments. Details on individual patients are provided in Table 1.

FIG. 3 Extent of interstitial lung disease



(**A**) Percentage changes in affected volume of lung parenchyma measured in high-resolution CT (HRCT) images as a percentage of total volume of lung parenchyma pre- and post-rituximab (Rtx) treatment for 23 ASS patients. The images were taken 0–3 months pre-Rtx and 3–12 months post-Rtx. (**B**) HRCT scan pre-Rtx (upper picture) and (**C**) post-Rtx (lower picture) for patient #18. A reticular pattern with innumerable interlacing streaks and distortion of the lung architecture is present in both lungs. The patient had 77% overall extent of interstitial lung disease pre-Rtx. Five months post-Rtx, only subtle interstitial thickening is visible posteriorly.

FIG. 4 Muscle outcome

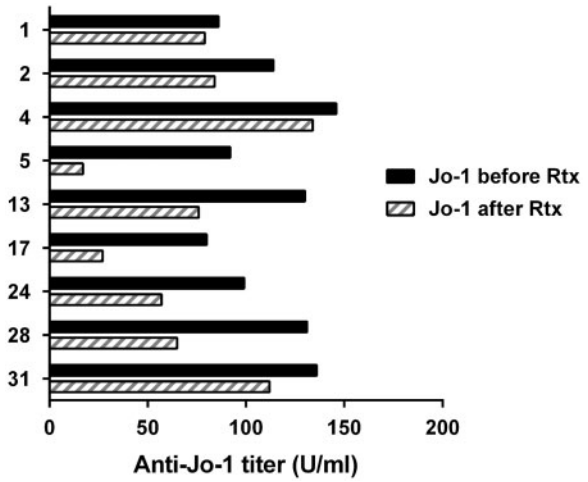


(**A**) Median changes in muscle activity measured as creatinine kinase levels in 16 ASS patients taken 0–2 months pre-rituximab (Rtx) and 3–6 months post-Rtx treatment. (**B**) Median changes in muscle strength measured by manual muscle test for eight muscles (MMT8) in 15 ASS patients pre- and post-Rtx treatment. The MMT8 results were obtained 0–3 months pre-Rtx and 3–30 months post-Rtx.

following treatment, indicating that Rtx has an effect on anti-Jo-1 homeostasis. Enumeration of $CD19^+$ cells was not done routinely; hence we do not know if anti-Jo-1 titre fluctuations correlated with repopulation of $CD19^+$ cells.

Our report has limitations. First, data collection was retrospective, and treatments were not given according to standardized protocols. Secondly, none of the patients were treated with Rtx as monotherapy. Combined induction therapy with CYC was used in patients with acute onset/exacerbation of ILD, and different kinds of maintentance therapy were started 0–3 months after the first Rtx cycle. Thus, our data do not allow for speculations about

FIG. 5 Serum anti-Jo-1 titres obtained before rituximab treatment, and 2–6 months after the treatment in nine ASS patients



Titres of serum anti-Jo-1 antibodies before and after rituximab (Rtx) treatment. The graph shows anti-Jo-1 levels obtained 0–3 months before Rtx and 2–6 months after Rtx in nine anti-synthetase syndrome patients.

the efficacy of Rtx as a single treatment for induction or maintenance therapy in ASS-associated ILD. Interestingly, data from Marie *et al*. [18] indicated that Rtx alone had an effect on ASS patients with refractory ILD. In their study, five out of seven patients (compared with 11 of 24 patients in this study) were refractory to CYC as monotherapy. In the study of Ingegnoli *et al*. [22] 4 of 8 CYC-treated patients with ASS-associated ILD deteriorated, as evaluated by HRCT-image analyses. This indicates that Rtx could be a treatment option in ASS patients with CYC-refractory ILD. However, from this study, no conclusions can be made on treatment regimen, Rtx either alone or in combination with CYC in ASS patients with severe ILD. A prospective study with two treatment arms (Rtx alone *vs* Rtx/CYC) could hopefully give some answers and is warranted.

This study is, to our knowledge, the first to report experience with Rtx in a large case series of ASS-related severe ILD with a median follow-up of >4 years. The results indicate that Rtx treatment could be of value in these patients, especially in those with short disease duration and/or acute onset/exacerbation of ILD, but SAEs, especially infections, remain an issue.

Acknowledgements

We thank Eli Taraldsrud at the Institute of Immunology, Oslo University Hospital, Oslo, Norway, for interpretation of the serology data.

Funding: This work was supported by grants from the Norwegian Women's Public Health Association and the Norwegian Rheumatology Patient Foundation.

Disclosure statement: The authors have declared no conflicts of interest.

References

1 Marguerie C, Bunn CC, Beynon HL *et al*. Polymyositis, pulmonary fibrosis and autoantibodies to aminoacyl-tRNA synthetase enzymes. Q J Med 1990;77:1019–38.

2 Mahler M, Miller FW, Fritzler MJ. Idiopathic inflammatory myopathies and the anti-synthetase syndrome: a comprehensive review. Autoimmun Rev 2014;13:367–71.

3 Hervier B, Devilliers H, Stanciu R *et al*. Hierarchical cluster and survival analyses of antisynthetase syndrome: phenotype and outcome are correlated with anti-tRNA synthetase antibody specificity. Autoimmun Rev 2012;12:210–7.

4 Kalluri M, Sahn SA, Oddis CV *et al*. Clinical profile of anti-PL-12 autoantibody. Cohort study and review of the literature. Chest 2009;135:1550–6.

5 Labirua A, Lundberg IE. Interstitial lung disease and idiopathic inflammatory myopathies: progress and pitfalls. Curr Opin Rheumatol 2010;22:633–8.

6 Chen IJ, Jan Wu YJ, Lin CW *et al*. Interstitial lung disease in polymyositis and dermatomyositis. Clin Rheumatol 2009;28:639–46.

7 Marie I, Josse S, Hatron PY *et al*. Interstitial lung disease in anti-Jo-1 patients with antisynthetase syndrome. Arthritis Care Res 2013;65:800–8.

8 Kotani T, Makino S, Takeuchi T *et al*. Early intervention with corticosteroids and cyclosporin A and 2-hour postdose blood concentration monitoring improves the prognosis of acute/subacute interstitial pneumonia in dermatomyositis. J Rheumatol 2008;35:254–9.

9 Marie I, Hatron PY, Dominique S *et al*. Short-term and long-term outcomes of interstitial lung disease in polymyositis and dermatomyositis: a series of 107 patients. Arthritis Rheum 2011;63:3439–47.

10 Morganroth PA, Kreider ME, Werth VP. Mycophenolate mofetil for interstitial lung disease in dermatomyositis. Arthritis Care Res 2010;62:1496–501.

11 Wilkes MR, Sereika SM, Fertig N, Lucas MR, Oddis CV. Treatment of antisynthetase-associated interstitial lung disease with tacrolimus. Arthritis Rheum 2005;52:2439–46.

12 Yamasaki Y, Yamada H, Yamasaki M *et al*. Intravenous cyclophosphamide therapy for progressive interstitial pneumonia in patients with polymyositis/dermatomyositis. Rheumatology 2007;46:124–30.

13 Basnayake C, Cash K, Blumbergs P, Limaye V. Use of rituximab in histologically confirmed idiopathic inflammatory myositis: a case series. Clin Rheumatol 2015;34:371–7.

14 Munoz-Beamud F, Isenberg DA. Rituximab as an effective alternative therapy in refractory idiopathic inflammatory myopathies. Clin Exp Rheumatol 2013;31:896–903.

15 Unger L, Kampf S, Luthke K, Aringer M. Rituximab therapy in patients with refractory dermatomyositis or polymyositis: differential effects in a real-life population. Rheumatology 2014;53:1630–8.

16 Oddis CV, Reed AM, Aggarwal R *et al*. Rituximab in the treatment of refractory adult and juvenile dermatomyositis and adult polymyositis: a randomized, placebo-phase trial. Arthritis Rheum 2013;65:314–24.

17 Aggarwal R, Bandos A, Reed AM *et al*. Predictors of clinical improvement in rituximab-treated refractory adult and juvenile dermatomyositis and adult polymyositis. Arthritis Rheumatol 2014;66:740–9.

18 Marie I, Dominique S, Janvresse A, Levesque H, Menard JF. Rituximab therapy for refractory interstitial lung disease related to antisynthetase syndrome. Respir Med 2012;106:581–7.

19 Levine TD. Rituximab in the treatment of dermatomyositis: an open-label pilot study. Arthritis Rheum 2005;52:601–7.

20 Nalotto L, Iaccarino L, Zen M *et al*. Rituximab in refractory idiopathic inflammatory myopathies and antisynthetase syndrome: personal experience and review of the literature. Immunol Res 2013;56:362–70.

21 Saketkoo LA, Mittoo S, Huscher D *et al*. Connective tissue disease related interstitial lung diseases and idiopathic pulmonary fibrosis: provisional core sets of domains and instruments for use in clinical trials. Thorax 2014;69:428–36.

22 Ingegnoli F, Lubatti C, Ingegnoli A *et al*. Interstitial lung disease outcomes by high-resolution computed tomography (HRCT) in Anti-Jo1 antibody-positive polymyositis patients: a single centre study and review of the literature. Autoimmun Rev 2012;11:335–40.

23 Sem M, Molberg O, Lund MB, Gran JT. Rituximab treatment of the anti-synthetase syndrome: a retrospective case series. Rheumatology 2009;48:968–71.

24 American Thoracic Society. Idiopathic pulmonary fibrosis: diagnosis and treatment. International consensus statement. American Thoracic Society (ATS), and the European Respiratory Society (ERS). Am J Respir Crit Care Med 2000;161 (2 Pt 1):646–64.

25 Bohan A, Peter JB. Polymyositis and dermatomyositis (second of two parts). N Engl J Med 1975;292:403–7.

26 Tillie-Leblond I, Wislez M, Valeyre D *et al*. Interstitial lung disease and anti-Jo-1 antibodies: difference between acute and gradual onset. Thorax 2008;63:53–9.

27 Quanjer PH, Tammeling GJ, Cotes JE *et al*. Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. Eur Respir J Suppl 1993;16:5–40.

28 Hansell DM, Bankier AA, MacMahon H *et al*. Fleischner Society: glossary of terms for thoracic imaging. Radiology 2008;246:697–722.

29 Aalokken TM, Lilleby V, Soyseth V *et al*. Chest abnormalities in juvenile-onset mixed connective tissue disease: assessment with high-resolution computed tomography and pulmonary function tests. Acta Radiol 2009;50:430–6.

30 Kendall FP, Mc Creary EK, Provance PG. Muscles: Testing and Function. 4th edn. Baltimore MD: Williams and Wilkins, 1993.

31 Sultan SM, Ng KP, Edwards JC, Isenberg DA, Cambridge G. Clinical outcome following B cell depletion therapy in eight patients with refractory idiopathic inflammatory myopathy. Clin Exp Rheumatol 2008;26:887–93.

32 Vandenbroucke E, Grutters JC, Altenburg J *et al*. Rituximab in life threatening antisynthetase syndrome. Rheumatol Int 2009;29:1499–502.

33 Aggarwal R, Cassidy E, Fertig N *et al*. Patients with non-Jo-1 anti-tRNA-synthetase autoantibodies have worse survival than Jo-1 positive patients. Ann Rheum Dis 2014;73:227–32.

34 Dugar M, Cox S, Limaye V, Blumbergs P, Roberts-Thomson PJ. Clinical heterogeneity and prognostic features of South Australian patients with anti-synthetase autoantibodies. Intern Med J 2011;41:674–9.